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Den Haag, den
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04. 11. 2004

Der Präsident des Europäischen Patentamts
Im Auftrag
For the President of the European Patent Office
Le Président de l'Office européen des brevets
p.o.

Marc Sertor

Patentanmeldung Nr.
Patent application no.
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PCT/EP 03/50220

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.: / Application no.: / Demande n°: PCT/EP 03/50220

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Bezeichnung der Erfindung: / Title of the invention: / Titre de l'invention: NOVEL FORMULATIONS FOR OPIOID-BASED TREATMENTS OF PAIN COMPRINSING SUBSTITUTED 1, 4-DI-PIPERIDIN-4-YL-PIPERAZINE DERIVATIVES

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NOVEL FORMULATIONS FOR OPIOID-BASED TREATMENTS OF PAIN COMPRISING SUBSTITUTED 1,4-DI-PIPERIDIN-4-YL-PIPERAZINE DERIVATIVES.

Field of the Invention

This invention concerns novel formulations for opioid-based treatments of pain and/or nociception comprising opioid analgesics and 1,4-di-piperidin-4-yl-piperazine derivatives having tachykinin antagonistic activity, in particular NK_1 antagonistic activity and the use of NK_1-receptor antagonists for the manufacture of a medicament for the prevention and/or treatment of respiratory depression in opioid-based treatments of pain as well as the use of an NK_1-receptor antagonist and an opioid analgesic for the manufacture of a medicament for the prevention and/or treatment of chronic neuropathic pain.

Background of The Invention

Opioid analgesics are the cornerstone of pain treatment, especially in the segment of moderate to severe acute and chronic pain. However, side-effects such as nausea/vomiting, constipation, respiratory depression and tolerance limit their use. The lowering of the high incidence of nausea and vomiting with many clinically used opioids is particularly considered as a major unmet medical need.

Tachykinins belong to a family of short peptides that are widely distributed in the mammalian central and peripheral nervous system (Bertrand and Geppetti, *Trends Pharmacol. Sci.* **17**:255-259 (1996) ; Lundberg, *Can. J. Physiol. Pharmacol.* **73**:908-914 (1995) ; Maggi, *Gen. Pharmacol* **26**:911-944 (1995) ; Regoli *et al.*, *Pharmacol. Rev.* **46** (1994)). They share the common C-terminal sequence Phe-Xaa-Gly-Leu-Met-NH_2. Tachykinins released from peripheral sensory nerve endings are believed to be involved in neurogenic inflammation. In the spinal cord/central nervous system, tachykinins may play a role in pain transmission/perception and in some autonomic reflexes and behaviours. The three major tachykinins are Substance P (SP), Neurokinin A (NK_A) and Neurokinin B (NK_B) with preferential affinity for three distinct receptor subtypes, termed NK_1, NK_2, and NK_3, respectively. However, functional studies on cloned receptors suggest strong functional cross-interaction between the 3 tachykinins and their corresponding receptors (Maggi and Schwartz, *Trends Pharmacol. Sci.* **18**: 351-355 (1997)). Species differences in structure of NK_1 receptors are responsible for species-related potency differences of NK_1 antagonists (Maggi, *Gen. Pharmacol.*

26:911-944 (1995) ; Regoli *et al.*, *Pharmacol. Rev.* **46(4)**:551-599 (1994)). The human NK_1 receptor closely resembles the NK_1 receptor of guinea-pigs and gerbils but differs markedly from the NK_1 receptor of rodents. The development of tachykinin antagonists has led to date to a series of peptide compounds of which might be anticipated that they are metabolically too labile to be employed as pharmaceutically active substances (Longmore J. *et al.*, *DN&P* **8(1)**:5-23 (1995)). NK_1-antagonists have been studied for a wide variety of indications including emesis, (stress-related) anxiety states, inflammatory responses, smooth muscle contraction and pain perception. NK_1-antagonists are in development for indications such as emesis, anxiety and depression, irritable bowel syndrome (IBS), circadian rhythm disturbances, visceral pain, neurogenic inflammation, asthma, micturition disorders, and nociception.

It has now been found that a particular class of compounds with predominantly NK_1-activity reduces to a large extent a number of unwanted side-effects associated with opioid analgesics, thereby increasing the total tolerability of said opioids in pain treatment, in particular in chronic neuropathic pain treatment. More specifically, respiratory depression and emesis is reduced in opioid-based treatments of pain. Also, due to the intrinsic antinociceptive activity of NK_1-antagonists, even some increase in opioid efficacy is noted, thereby creating the option to reduce the opioid dose without effecting its analgesic action.

Background prior art

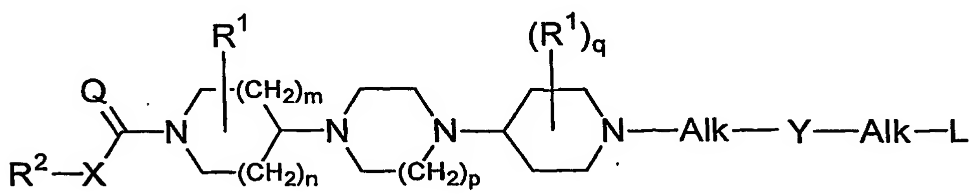
Compounds containing the 1-piperidin-4-yl-piperazinyl moiety were disclosed in WO 97/16440-A1, published May 9, 1997 by Janssen Pharmaceutica N.V. for use as substance P antagonists, in WO 02/32867, published April 25, 2002 by Glaxo Group Ltd. for their special advantages as tachykinin antagonists (more specifically were disclosed 4-piperazin-1-yl-piperidine-1-carboxylic acid amide derivatives), in WO 01/30348-A1, published May 03, 2001 by Janssen Pharmaceutica N.V., for use as substance P antagonists for influencing the circadian timing system, and in WO 02/062784-A1, published August 15, 2002 by Hoffmann-La Roche AG for use as NK_1 antagonists.

Formulations containing NK_1-antagonists and opioid analgesics for the prevention and/or treatment of pain and/or nociception are disclosed in WO 96/20009 (Merck, July 4, 1996) and WO 97/25988 (Eli Lilly, July 24, 1997). There is no mentioning of the reduction of side-effects apart from emesis.

The compounds of the present invention differ from the compounds of the prior art in the substitution of the piperazinyl moiety, being a substituted piperidinyl moiety as well as in their improved ability as potent, orally and centrally active tachykinin antagonists with therapeutic value in combinations with opioid analgesics for reduction of opioid-induced side-effects and increasing the tolerability of said opioids.

Description of the Invention

The present invention relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredients, a therapeutically effective amount of an opioid analgesic and a compound according to Formula (I)



(I)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof, wherein :

n	is an integer, equal to 0, 1 or 2 ;
m	is an integer, equal to 1 or 2, provided that if m is 2, then n is 1 ;
p	is an integer equal to 1 or 2 ;
Q	is O or NR^3 ;
X	is a covalent bond or a bivalent radical of formula -O-, -S- or $-NR^3-$;
each R^3	independently from each other, is hydrogen or alkyl ;
each R^1	independently from each other, is selected from the group of Ar^1, Ar^1-alkyl and di(Ar^1)-alkyl ;
q	is an integer equal to 0 or 1 ;
R^2	is alkyl, Ar^2, Ar^2-alkyl, Het^1 or Het^1-alkyl ;
Y	is a covalent bond or a bivalent radical of formula -C(=O)- or $-SO_2-$;
each Alk	represents, independently from each other, a covalent bond; a bivalent straight or branched, saturated or unsaturated hydrocarbon radical having from 1 to 6 carbon atoms ; or a cyclic saturated or unsaturated hydrocarbon radical having from 3 to 6 carbon atoms ; each radical optionally substituted on one or more carbon atoms with one or more alkyl, phenyl, halo, cyano, hydroxy, formyl and amino radicals ;
L	is selected from the group of hydrogen, alkyloxy, Ar^3-oxy, alkyloxycarbonyl, mono- and di(alkyl)amino, mono-and di(Ar^3)amino, Ar^3,

Ar^3-carbonyl, Het^2 and Het^2-carbonyl;

Ar^1 is phenyl, optionally substituted with 1, 2 or 3 substituents each independently from each other selected from the group of halo, alkyl, cyano, aminocarbonyl and alkyloxy ;

Ar^2 is naphthalenyl or phenyl, each optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, nitro, amino, mono- and di(alkyl)amino, cyano, alkyl, hydroxy, alkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl and mono- and di(alkyl)aminocarbonyl ;

Ar^3 is naphthalenyl or phenyl, optionally substituted with 1, 2 or 3 substituents each independently from each other selected from the group of alkyloxy, alkyl, halo, hydroxy, pyridinyl, morpholinyl, pyrrolidinyl, imidazo[1,2-*a*]pyridinyl, morpholinylcarbonyl, pyrrolidinylcarbonyl, amino and cyano;

Het^1 is a monocyclic heterocyclic radical selected from the the group of pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl ; or a bicyclic heterocyclic radical selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl ; each heterocyclic radical may optionally be substituted on any atom by a radical selected from the group of halo and alkyl ;

Het^2 is a monocyclic heterocyclic radical selected from the group of pyrrolidinyl, dioxolyl, imidazolidinyl, pyrrazolidinyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, imidazolidinyl, tetrahydrofuranyl, 2H-pyrrolyl, pyrrolinyl, imidazolinyl, pyrrazolinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl ; or a bicyclic heterocyclic radical selected from the group of benzopiperidinyl, quinolinyl, quinoxalinyl, indolyl, isoindolyl, chromenyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl ; each radical optionally substituted with one or more radicals selected from the group of Ar^1, Ar^{1}alkyl, halo, hydroxy, alkyl, piperidinyl, pyrrolyl, thienyl, oxo, alkyloxy, alkyloxyalkyl and alkyloxycarbonyl ; and

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radicals having from 3 to 6

carbon atoms ; optionally substituted on one or more carbon atoms with one or more radicals selected from the group of phenyl, halo, cyano, oxo, hydroxy, formyl and amino radicals .

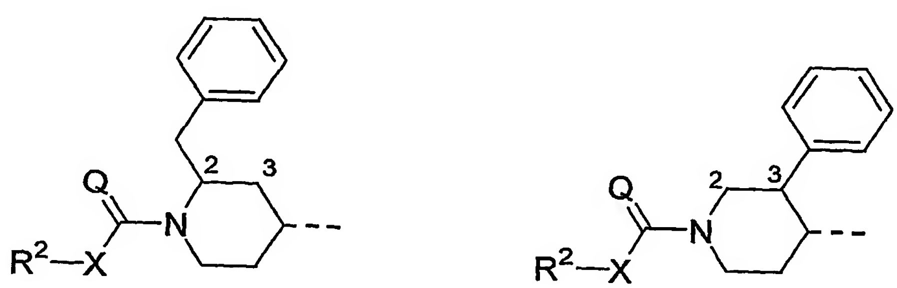
More in particular, the invention relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredients, an opioid analgesic and a therapeutically effective amount of a compound according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein :

n	is 1 ;
m	is 1 ;
p	is 1 ;
Q	is O ;
X	is a covalent bond ;
each R^1	is Ar^1 or Ar^1-alkyl ;
q	is 0 or 1 ;
R^2	is Ar^2 ;
Y	is a covalent bond or a bivalent radical of formula -C(=O)- or -SO_2- ;
each Alk	represents, independently from each other, a covalent bond; a bivalent straight or branched, saturated or unsaturated hydrocarbon radical having from 1 to 6 carbon atoms ; or a cyclic saturated or unsaturated hydrocarbon radical having from 3 to 6 carbon atoms ; each radical optionally substituted on one or more carbon atoms with one or more phenyl, halo, cyano, hydroxy, formyl and amino radicals ;
L	is selected from the group of hydrogen, alkyloxy, Ar^3-oxy, alkyloxycarbonyl, mono- and di(alkyl)amino, mono-and di(Ar^3)amino, Ar^3 and Het^2;
Ar^1	is phenyl, optionally substituted with 1, 2 or 3 alkyl radicals ;
Ar^2	is phenyl, optionally substituted with 1, 2 or 3 alkyl radicals ;
Ar^3	is phenyl, optionally substituted with 1, 2 or 3 substituents each independently from each other selected from the group of alkyloxy, alkyl, halo, hydroxy, pyridinyl, morpholinyl, pyrrolidinyl, imidazo[1,2-*a*]pyridinyl, morpholinylcarbonyl, pyrrolidinylcarbonyl, amino and cyano ;
Het^2	is a monocyclic heterocyclic radical selected from the group of pyrrolidinyl, piperidinyl, morpholinyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, isoxazolyl, thiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl ; or a bicyclic heterocyclic radical selected from the group of

benzopiperidinyl, quinolinyl, quinoxalinyl, indolyl, chromenyl and benzimidazolyl ; each radical optionally substituted with one or more radicals selected from the group of Ar^1, Ar^1alkyl, halo, hydroxy, alkyl, piperidinyl, pyrrolyl, thienyl, oxo and alkyloxycarbonyl ; and

alkyl is a straight hydrocarbon radical having 1 to 6 carbon atoms, optionally substituted with one or more halo radicals ;

More in particular, the invention relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredients, an opioid analgesic and a therapeutically effective amount of a compound according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein R^1 is Ar^1methyl and attached to the 2-position or R^1 is Ar^1 and attached to the 3-position, as exemplified in either of the following formulas for compounds according to Formula (I) wherein m and n are equal to 1 and Ar is an unsubstituted phenyl. Preferably, Ar^1methyl is an unsubstituted benzyl radical.



More in particular, the pharmaceutical composition comprises a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein the R^2-X-C(=Q)- moiety is 3,5-di-(trifluoromethyl) phenylcarbonyl.

In the framework of this application, alkyl is defined as a monovalent straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms, for example methyl, ethyl, propyl, butyl, 1-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl ; alkyl further defines a monovalent cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, for example cyclopropyl, methylcyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The definition of alkyl also comprises an alkyl radical that is optionally substituted on one or more carbon atoms with one or more phenyl, halo, cyano, oxo,

hydroxy, formyl and amino radicals, for example hydroxyalkyl, in particular hydroxymethyl and hydroxyethyl and polyhaloalkyl, in particular difluoromethyl and trifluoromethyl.

In the framework of this application, halo is generic to fluoro, chloro, bromo and iodo.

In the framework of this application, especially in the moiety Alk^a-Y-Alk^b in Formula (I), when two or more consecutive elements of said moiety denote a covalent bond, then a single covalent bond is denoted. For example, when Alk^a and Y denote both a covalent bond and Alk^b is CH_2, then the moiety Alk^a-Y-Alk^b denotes -CH_2.

The pharmaceutically acceptable salts are defined to comprise the therapeutically active non-toxic acid addition salts forms that the compounds according to Formula (I) are able to form. Said salts can be obtained by treating the base form of the compounds according to Formula (I) with appropriate acids, for example inorganic acids, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid ; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclamic acid, salicylic acid, p-aminosalicylic acid and pamoic acid.

The compounds according to Formula (I) containing acidic protons may also be converted into their therapeutically active non-toxic metal or amine addition salts forms by treatment with appropriate organic and inorganic bases. Appropriate base salts forms comprise, for example, the ammonium salts, the alkaline and earth alkaline metal salts, in particular lithium, sodium, potassium, magnesium and calcium salts, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hybramine salts, and salts with amino acids, for example arginine and lysine.

Conversely, said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

The term addition salt as used in the framework of this application also comprises the solvates that the compounds according to Formula (I) as well as the salts thereof, are able to form. Such solvates are, for example, hydrates and alcoholates.

The *N*-oxide forms of the compounds according to Formula (I) are meant to comprise those compounds according to Formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein one or more tertiary nitrogens (e.g of the piperazinyl or piperidinyl radical) are *N*-oxidized. Such *N*-oxides can easily be obtained by a skilled person without any inventive skills and they are obvious alternatives for the compounds according to Formula (I) since these compounds are metabolites, which are formed by oxidation in the human body upon uptake . As is generally known, oxidation is normally the first step involved in drug metabolism (Textbook of Organic Medicinal and Pharmaceutical Chemistry, 1977, pages 70- 75). As is also generally known, the metabolite form of a compound can also be administered to a human instead of the compound per se, with much the same effects.

The compounds according to Formula (I) possess at least 2 oxydizable nitrogens (tertiary amines moieties). It is therefore highly likely that *N*-oxides are to form in the human metabolism.

The compounds according to Formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material according to Formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms that the compounds according to Formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on

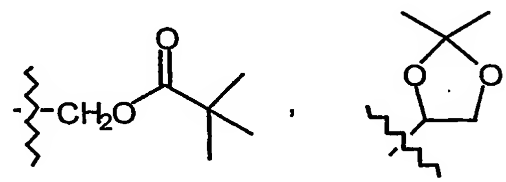
bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds according to Formula (I) are obviously intended to be embraced within the scope of this invention.

Following CAS nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a molecule, an *R* or *S* descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. The configuration of the second stereogenic center is indicated using relative descriptors *[R*,R*]* or *[R*,S*]*, where R* is always specified as the reference center and [*R*,R**] indicates centers with the same chirality and [*R*,S**] indicates centers of unlike chirality. For example, if the lowest-numbered chiral center in the molecule has an *S* configuration and the second center is *R*, the stereo descriptor would be specified as *S*-[*R*,S**]. If "α" and "β" are used : the position of the highest priority substituent on the asymmetric carbon atom in the ring system having the lowest ring number, is arbitrarily always in the "α" position of the mean plane determined by the ring system. The position of the highest priority substituent on the other asymmetric carbon atom in the ring system (hydrogen atom in compounds according to Formula (I)) relative to the position of the highest priority substituent on the reference atom is denominated "α", if it is on the same side of the mean plane determined by the ring system, or "β", if it is on the other side of the mean plane determined by the ring system.

Compounds according to Formula (I) and some of the intermediate compounds have at least two stereogenic centers in their structure.

The invention also comprises pharmaceutical compositions according to the invention comprising derivative compounds (usually called "pro-drugs") of the pharmacologically-active compounds according to the invention, which are degraded *in vivo* to yield the compounds according to the invention. Pro-drugs are usually (but not always) of lower potency at the target receptor than the compounds to which they are degraded. Pro-drugs are particularly useful when the desired compound has chemical or physical properties that make its administration difficult or inefficient. For example, the desired compound may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion on pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs*, 1985, **29**, pp. 455-473.

Pro-drugs forms of the pharmacologically-active compounds according to the invention will generally be compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the *N*-oxide form thereof, having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the formula $-COOR^x$, where R^x is a C_{1-6}alkyl, phenyl, benzyl or one of the following groups :



Amidated groups include groups of the formula $-CONR^yR^z$, wherein R^y is H, C_{1-6}alkyl, phenyl or benzyl and R^z is $-OH$, H, C_{1-6}alkyl, phenyl or benzyl. Compounds according to the invention having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This base will hydrolyze with first order kinetics in aqueous solution.

The compounds according to Formula (I) as prepared in the processes described below may be synthesized in the form of racemic mixtures of enantiomers that can be separated from one another following art-known resolution procedures. The racemic compounds according to Formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds according to Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

Suitable opioid analgesics of use in the present invention include alfentanil, buprenorphine, butorphanol, codeine, diacetylmorphine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine,

nalbuphine, oxycodone, oxymorphone, pentazocine, propoxyphene and sufentanyl; or a pharmaceutical acceptable salt thereof.

Because of their widespread use as analgesics and because they represent two completely different chemical classes of agents with different physicochemical and pharmaco-dynamic properties, preferred opioid analgesics of use in the present invention are morphine and fentanyl ; or pharmaceutical acceptable salts thereof.

Suitable pharmaceutically acceptable salts of the opioid analgesics of use in the present invention include those salts described above in relation to the salts of the NK_1-antagonist.

Preferred salts of opioid analgesics of use in the present invention include alfentanyl hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, codeine phosphate, codeine sulphate, diacetylmorphine hydrochloride, dihydrocodeine bitartrate, fentanyl citrate, hydrocodone bitartrate, hydromorphone hydrochloride, levorphanol tartrate, meperidine hydrochloride, methadone hydrochloride, morphine sulphate, morphine hydochloride, morphine tartrate, nalbuphine hydrochloride, oxymorphone hydrochloride, pentazocine hydrochloride, propoxyphene hydrochloride and propoxyphene napsylate (2-naphthalene sulphonic acid (1:1) monohydrate).

Particular preferred opioid analgesics of use in the present invention are morphine sulphate and fentanyl citrate

Pharmacology

The compounds according to Formula (I) are potent inhibitors of neurokinin-mediated effects, in particular those mediated via the NK_1 receptor, and may therefore be described as tachykinin antagonists, especially as substance P antagonists, as indicated *in vitro* by the antagonism of substance P-induced relaxation of pig coronary arteries which is described hereinafter. The binding affinity of the present compounds for the human, guinea-pig and gerbil neurokinin receptors may be determined *in vitro* in a receptor binding test using ^{3}H-substance-P as radioligand. The subject compounds also show substance-P antagonistic activity *in vivo* as may be evidenced by, for instance, the antagonism of substance P-induced plasma extravasation in guinea-pigs, or the antagonism of drug-induced emesis in ferrets (Watson *et al.*, *Br. J. Pharmacol.* **115**:84-94 (1995)).

The combination of an opioid analgesic with an NK_1 antagonist results in improved efficacy. Additional to the gain in efficacy, this combination also reduces several of the side-effects currently present with clinically used opioids. NK_1 receptor antagonists potentiating the analgesic activity of opioids require lower doses, resulting in a reduced risk of opioid side-effects.

The compounds according to Formula (I) have shown to reduce unwanted side-effects induced by opioids. Such reduction can be tested by *in vivo* testing using several species (e.g. ferrets, gerbils, rats, guinea pigs) and several pain models, covering different states of acute and chronic pain. For instance, the compounds of the present invention :

- were able to inhibit the opioid-induced emesis in several species;
- did not affect the antinociceptive properties of opioids in models of acute, visceral and high intensity pain;
- had an additive effect on the antinociceptive properties of opioids in models of inflammatory and chronic neuropathic pain;
- reduced the respiratory depression induced by opioids in several species;
- were able to overcome the tolerance observed with opioids daily administered in a model of chronic neuropathic pain;
- did not interfere with the discriminative central narcotic effects of opioids;
- had no effect on the pharmacokinetics of opioids when administered concomitantly. This excludes pharmacokinetic interactions as the origin of the pharmacological effects observed.

The present invention therefor also relates to the use of an NK_1-receptor antagonist, in particular an NK_1-receptor antagonist according to Formula (I), for the manufacture of a medicament for the prevention and/or treatment of respiratory depression in opioid-based treatments of pain.

The present invention further relates to the use of a pharmaceutical composition according to the invention for the manufacture of a medicament for the prevention and/or treatment of pain and/or nociception.

The present invention further relates to the use of a pharmaceutical composition according to the invention for the manufacture of a medicament for the prevention and/or treatment of chronic neuropathic pain.

The present invention further relates to the use of a pharmaceutical composition

according to the invention or the use of an NK1-receptor antagonist according to Formula (I) and an opioid analgesic for the manufacture of a medicament for the prevention and/or treatment of emesis in opioid-based treatments of pain.

To prepare the pharmaceutical compositions of this invention, an effective amount of the active ingredient, optionally in addition salt form, is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. The pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally, rectally, percutaneously, by parenteral injection or by inhalation. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical

carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

The NK_1-receptor antagonist and the opioid analgesic may be formulated in a single pharmaceutical composition or alternatively in individual pharmaceutical compositions for simultaneous, separate or sequential use in accordance with the present invention. The pharmaceutical composition may also be a product comprising the NK_1-receptor antagonist and the opioid analgesic as separate unit dosages.

When administered in combination, either as a single or as separate pharmaceutical composition(s), the NK_1-receptor antagonist and the opioid analgesic are presented in a ratio which is consistent with the manifestation of the desired effect. In particular, the ratio by weight of the NK_1-antagonist to the opioid analgesic will suitably be approximately 1 to 1. Preferably, this ratio will be between 0.001 to 1 and 1000 to 1, and especially between 0.01 to 1 and 100 to 1.

A suitable dosage level for the NK_1-receptor antagonist is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg day. The compounds may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day.

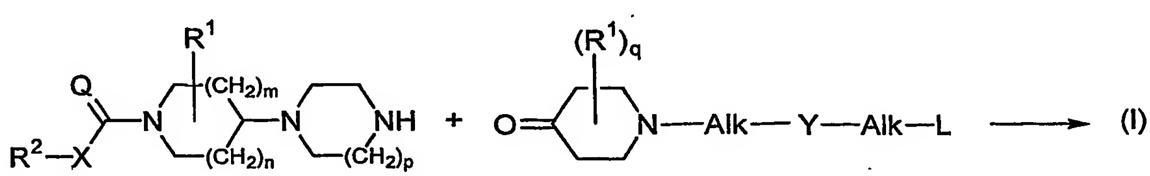
The opioid analgesic may be administered at a dosage level up to conventional dosage levels for such analgesics, but preferably at a reduced level in accordance with the present invention. Suitable dosage levels will depend upon the analgesic effect of the chosen opioid analgesic, but typically suitable levels will be about 0.001 to 25 mg/kg per day, preferably 0.005 to 10 mg/kg per day, and especially 0.005 to 5 mg/kg day. The compound may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day.

It will be appreciated that the amount of an NK_1-receptor antagonist and an opioid analgesic required for use in the prevention and/or treatment of pain and nociception will vary not only with the particular compounds or compositions selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the human in need of such a treatment, and will ultimately be at the discretion of the attendant physician.

<u>Chemistry</u>

The compounds according to the invention can generally be prepared by a succession of steps, each of which is known to the skilled person.

The compounds according to Formula (I) are conveniently prepared by reductively N-alkylating an intermediate of Formula (II) with and intermediate of Formula (III). Said reductive N-alkylation may be performed in a reaction-inert solvent such as, for example, dichloromethane, ethanol or toluene or a mixture thereof, and in the presence of an appropriate reducing agent such as, for example, a borohydride, e.g. sodium borohydride, sodium cyanoborohydride or triacetoxy borohydride. In case a borohydride is used as a reducing agent, it may be convenient to use a complex-forming agent such as, for example, titanium(IV)isopropylate as described in J. Org. Chem, 1990, *55*, 2552-2554. Using said complex-forming agent may also result in an improved *cis/trans* ratio in favour of the *trans* isomer. It may also be convenient to use hydrogen as a reducing agent in combination with a suitable catalyst such as, for example, palladium-on-charcoal or platinum-on-charcoal. In case hydrogen is used as reducing agent, it may be advantageous to add a dehydrating agent to the reaction mixture such as, for example, aluminium *tert*-butoxide. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may also be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene or quinoline-sulphur. Stirring and optionally elevated temperatures and/or pressure may enhance the rate of the reaction.



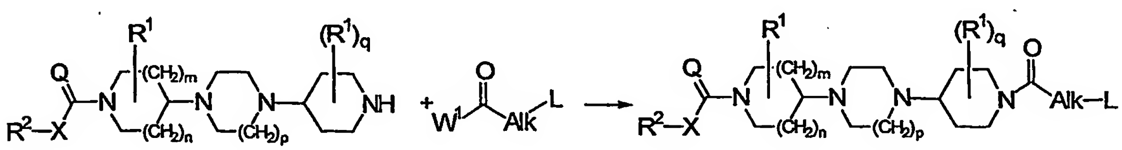
(II) (III)

In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, trituration and chromatography.

Especially advantage is the preparation of a compound according to the invention according to the previous reaction scheme in which the Alk-Y-Alk-L-moiety is benzyl, thus giving rise to a compound according to Formula (I) in which the Alk-Y-Alk-L-

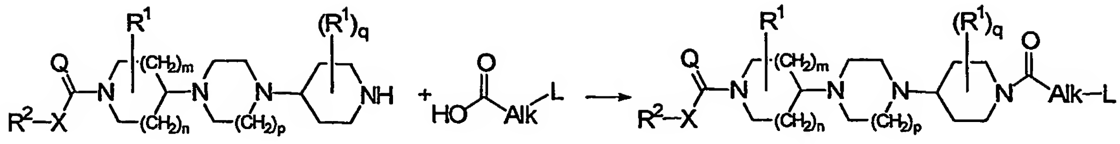
moiety is benzyl. Said compound is pharmacological active and can be converted into a compound according to the invention in which the Alk-Y-Alk-L-moiety is hydrogen by reductive hydrogenation using e.g. hydrogen as a reducing agent in combination with a suitable catalyst such as, for example, palladium-on-charcoal or platinum-on-charcoal. The resulting compound according to the invention can then be converted into other compounds according to the invention by art-known transformations, e.g. acylation and alkylation.

In particular, the compounds according to Formula (I^a) can be prepared by reacting a final compound of Formula (I') with an intermediate of Formula (V) wherein W^1 is an appropriate leaving group such as, for example, a halogen, e.g. chloro or bromo, or a sulfonyloxy leaving group, e.g. methanesulfonyloxy or benzenesulfonyloxy. The reaction can be performed in a reaction-inert solvent such as, for example, a chlorinated hydrocarbon, e.g. dichloromethane, an alcohol, e.g. ethanol, or a ketone, e.g. methyl isobutylketone, and in the presence of a suitable base such as, for example, sodium carbonate, sodium hydrogen carbonate or triethylamine. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried at a temperature ranging between room temperature and reflux temperature.



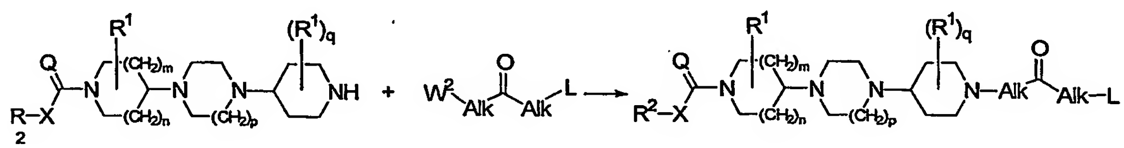
(I') (V) (I^a)

Alternatively, the compounds according to Formula (I^a) can also be prepared by reacting a final compound of Formula (I') with a carboxylic acid of Formula (VI). The reaction can be performed in a reaction-inert solvent such as, for example, a chlorinated hydrocarbon, e.g. dichloromethane, an alcohol, e.g. ethanol, or a ketone, e.g. methyl isobutylketone, and in the presence of a suitable base such as, for example, sodium carbonate, sodium hydrogen carbonate or triethylamine. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried at a temperature ranging between room temperature and reflux temperature.



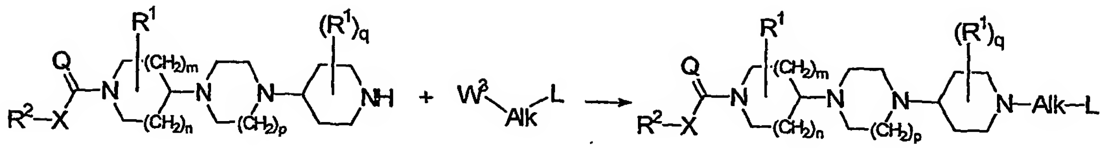
(I') (VI) (I^a)

In particular, the compounds according to Formula (I^b) can be prepared by reacting a final compound of Formula (I') with a compound of Formula (VII) wherein W^2 is an appropriate leaving group such as, for example, a halogen, e.g. chloro or bromo, or a sulfonyloxy leaving group, e.g. methanesulfonyloxy or benzenesulfonyloxy. The reaction can be performed in a reaction-inert solvent such as, for example, a chlorinated hydrocarbon, e.g. dichloromethane, an alcohol, e.g. ethanol, or a ketone, e.g. methyl isobutylketone, and in the presence of a suitable base such as, for example, sodium carbonate, sodium hydrogen carbonate or triethylamine. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried at a temperature ranging between room temperature and reflux temperature.



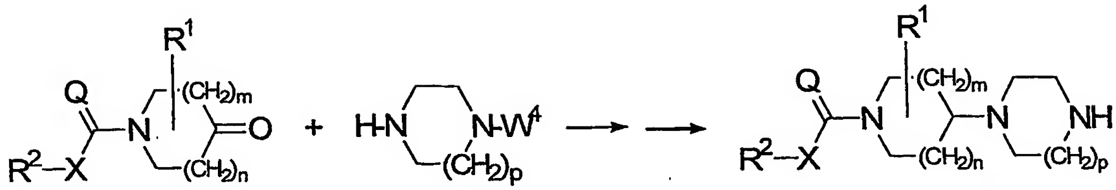
(I') (VII) (I^b)

The compounds according to Formula (I^c) can be prepared by reductive amination /alkylation of a final compound of Formula (I') with a compound of Formula (VIII) wherein W^3 is an appropriate leaving group such as, for example, a halogen, e.g. chloro or bromo, or a sulfonyloxy leaving group, e.g. methanesulfonyloxy or benzenesulfonyloxy. The reaction can be performed in a reaction-inert solvent such as, for example, a chlorinated hydrocarbon, e.g. dichloromethane, an alcohol, e.g. ethanol, or a ketone, e.g. methyl isobutylketone, and in the presence of a suitable base such as, for example, sodium carbonate, sodium hydrogen carbonate or triethylamine. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried at a temperature ranging between room temperature and reflux temperature.



(I')　　(VIII)　　(I^c)

The starting materials and some of the intermediates are known compounds and are commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, intermediates of formula (II) may be prepared by reductively *N*-alkylating an intermediate of formula (IX) with an intermediate of formula (X) in which W^4 is a benzyl radical, after which the compound according to Formula (X) is subsequently reduced to yield an intermediate compound according to Formula (II). Said reductive *N*-alkylation may be performed in a reaction-inert solvent such as, for example, dichloromethane, ethanol, toluene or a mixture thereof, and in the presence of an appropriate reducing agent such as, for example, a borohydride, e.g. sodium borohydride, sodium cyanoborohydride or triacetoxy borohydride. In case a borohydride is used as a reducing agent, it may be convenient to use a complex-forming agent such as, for example, titanium(IV)isopropylate as described in J. Org. Chem, 1990, *55*, 2552-2554. Using said complex-forming agent may also result in an improved *cis*/*trans* ratio in favour of the *trans* isomer. It may also be convenient to use hydrogen as a reducing agent in combination with a suitable catalyst such as, for example, palladium-on-charcoal or platinum-on-charcoal. In case hydrogen is used as reducing agent, it may be advantageous to add a dehydrating agent to the reaction mixture such as, for example, aluminium *tert*-butoxide. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may also be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene or quinoline-sulphur. Stirring and optionally elevated temperatures and/or pressure may enhance the rate of the reaction.



(IX) (X) (II)

The preparation of these and other intermediates is described in WO 97/16440-A1, published May 9, 1997 by Janssen Pharmaceutica N.V, which is disclosed herein by reference as well as in other publications mentioned in WO 97/16440-A1, such as , e.g. EP-0,532,456-A.

The following examples are intended to illustrate and not to limit the scope of the present invention.

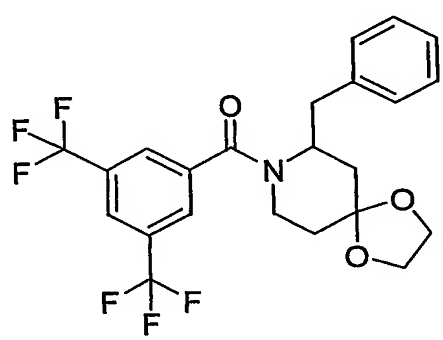
Experimental Part

Hereinafter "RT" means room temperature, "THF" means tetrahydrofuran, "DIPE" means diisopropylether, "DCM" means dichloromethane and "DMF" means *N,N*-dimethylformamide.

Preparation of the intermediate compounds

Example A1

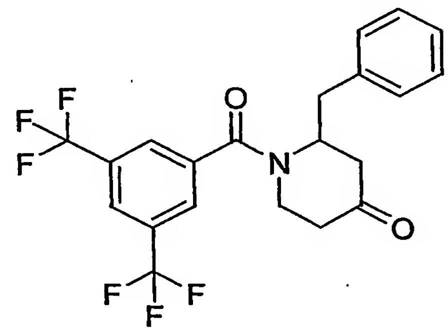
a. Preparation of intermediate compound 1



Et_3N (0.55 mol) was added to a stirring mixture of 7-(phenylmethyl)-1,4-dioxa-8-azaspiro[4.5]decane (0.5 mol) in toluene (1500ml). 3,5-Bis(trifluoromethyl)benzoyl chloride (0.5 mol) was added over a 1-hour period (exothermic reaction). The mixture was stirred at room temperature for 2 hours, then allowed to stand for the weekend and washed three times with water (500ml, 2x250ml). The organic layer was separated, dried, filtered and the solvent was evaporated. Yielding: 245g (100%). Part of this

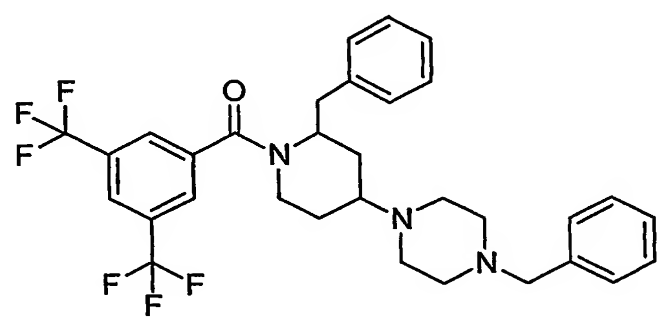
fraction was crystallized from petroleum ether. The precipitate was filtered off and dried. Yielding: 1.06g of intermediate compound 1.

b. Preparation of intermediate compound 2



HCl cp (300 ml) was added to a mixture of intermediate compound 1 (0.5 mol) in ethanol (300 ml) and H_2O (300 ml). The reaction mixture was stirred at 60 °C for 20 hours. The precipitate was filtered off, ground, stirred in H_2O, filtered off, washed with petroleum ether and dried. Yielding: 192 g of intermediate compound 2 ((+-)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinone) (89.4%) (mixture of R and S enantiomers).

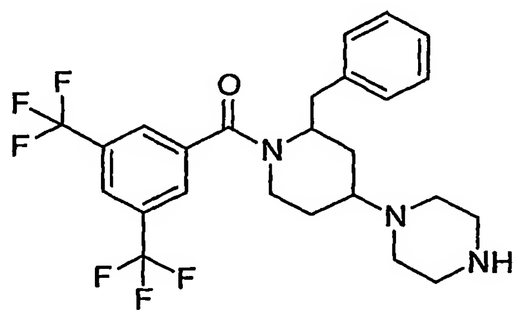
c. Preparation of intermediate compound 3



A mixture of intermediate compound 2 (0.046 mol), 1-(phenylmethyl)piperazine (0.051 mol) and C (0.056 mol) was stirred for 2 hours at 40 °C. The reaction mixture was cooled to room temperature. Ethanol, p.a. (350 ml) was added. BH_4Na (0.138 mol) was added. The resulting reaction mixture was stirred for one hour at room temperature, then for one hour at 50 °C. More BH_4Na (5.2 g) was added and the reaction mixture was stirred for 2 hours at 50 °C. Again, BH_4Na was added and the reaction mixture was stirred overnight at room temperature, then for 2 hours at 50 °C. Water (10 ml) was added. The mixture was stirred for 15 min. CH_2Cl_2 (200 ml) was added and the mixture was stirred for 15 min. The organic phase was separated, dried ($MgSO_4$), dicalite was added, the mixture was filtered over dicalite, and the filtrate was evaporated. This fraction was separated into (CIS) and (TRANS) by column chromatography over silica gel. The desired (TRANS)-fractions were collected and the solvent was evaporated,

giving 14.8 g of residue ((I), 1.06% (CIS)) and 4.9 g of residue ((II), 6% (CIS)). Resolution and purification of those (TRANS)-fractions (± 20 g in total) was obtained by chromatography over stationary phase Chiralcel OD (1900Gr) in Prochrom LC110 35 bar (eluent: hexane/ethanol 90/10). The desired fractions were collected and the solvent was evaporated. Yielding: 9.5 g of intermediate compound 3 (2R-trans)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-[4-(phenylmethyl)-1-piperazinyl]piperidine.

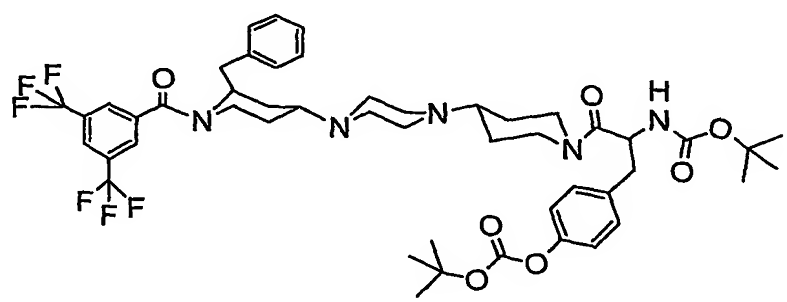
d. Preparation of intermediate compound 4



A mixture of intermediate compound 3 (0.288 mol) in methanol (700 ml) was hydrogenated at 40 °C with Pd/C, 10% (5 g) as a catalyst. After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated. Yielding: 141.2 g of intermediate compound 4 (+)-(2R-trans)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-(1-piperazinyl)piperidine.

Example A2

Preparation of intermediate compound 5

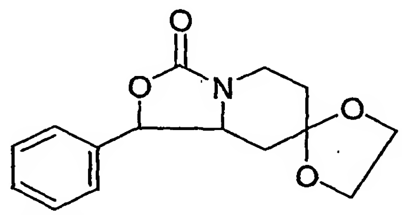


A mixture of *N*-[(1,1-dimethylethoxy)carbonyl]-L-tyrosine 1,1-dimethylcarbonate (0.005 mol), *N,N*-dimethyl-4-pyridinamine (0.006 mol) and Et_3N (0.006 mol) in CH_2Cl_2, p.a. (10ml) was stirred at room temperature. *N*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine monohydrochloride (0.006 mol) was added portionwise and was stirred for 45 minutes at room temperature. Then final compound 2 (described in example B1.b) (0.005 mol) was added and the reaction mixture was stirred overnight at room temperature. The mixture was washed with H_2O and Na_2CO_3. The separated organic

layer was dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent : CH_2Cl_2/MeOH 100/0;98/2;96/4;94/6). The purest fractions were collected and the solvent was evaporated Yield : 1.4g intermediate compound 5 (30%).

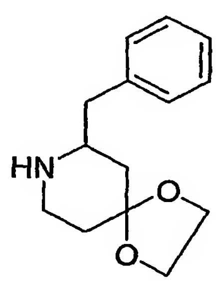
Example A3

a. Preparation of intermediate compound 6



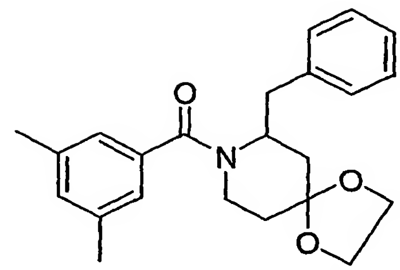
A mixture of 7-(hydroxyphenylmethyl)-1,4-dioxa-8-azaspiro[4,5]decane-8-carboxylic acid 1,1-dimethylethyl ester (0.5 mol) and 2-methyl-2-propanol potassium salt (6g) in toluene (900ml) was stirred and refluxed for 2h. The mixture was evaporated and the residue was stirred up in petrol ether and a little water. The mixture was decanted and the residue was stirred up in DIPE. The precipitate was filtered off and dried. Yielding : 127.4g of intermediate compound 6 (92%).

b. Preparation of intermediate compound 7



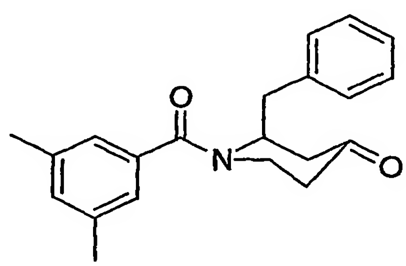
A mixture of intermediate compound 6 (0.5 mol) in methanol (700ml) was hydrogenated at 50°C overnight with Pd/C, 10% (5g) as a catalyst. After uptake of H_2 (1eq), the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in water and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered off and evaporated. Yielding : 99g intermediate compound 7 (85%).

c. Preparation of intermediate compound 8



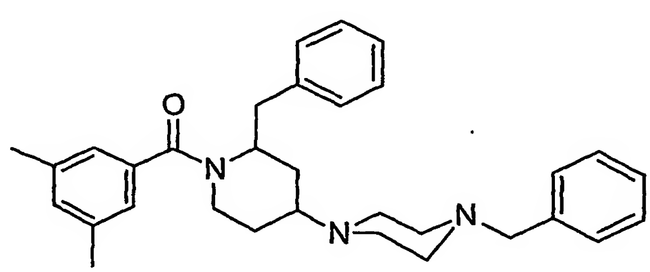
Et_3N (0.55 mol) was added to a mixture of intermediate compound 7 (0.5 mol) in toluene (1500ml). 3,5-Dimethylbenzoyl chloride (0.5 mol) was added dropwise slowly over a 1-hour period while the temperature was kept below 50°C and while stirring was continued. The mixture was stirred at room temperature overnight, then washed three times with water (500ml, 2x250ml) and separated into its layers. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. Yielding: 197g (113%). Part of this fraction was dried. Yielding: 0.65g of intermediate compound 8.

d. Preparation of intermediate compound 9



A mixture of intermediate compound 8 (0.56 mol) in ethanol (300ml), HCl (300ml) and H_2O (300ml) was stirred at 60°C for 8 hours. The mixture was stirred at room temperature for the weekend. The precipitate was filtered off, taken up in water, filtered off, washed with petroleum ether and dried. Yielding: 140.9g of intermediate compound 9 (88%).

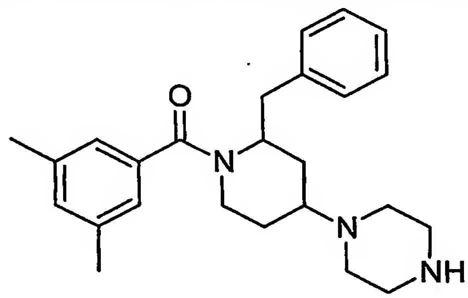
e. Preparation of intermediate compound 10



A mixture of intermediate compound 9 (0.05 mol) and 1-(phenylmethyl)-piperazine (0.05 mol) in thiophene, 4% solution (2ml) and toluene (500ml) was hydrogenated with Pd/C, 10% (1g) as a catalyst. After uptake of H_2 (1eq), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over

silica gel (eluent : $CH_2Cl_2/(CH_3OH/NH_3)$ 99/1). The pure fractions were collected and evaporated. Yielding : 17.07g (71%).. The pure fractions of fraction 1 were collected and evaporated. Yielding : 2.5g of intermediate compound 10 (10%).

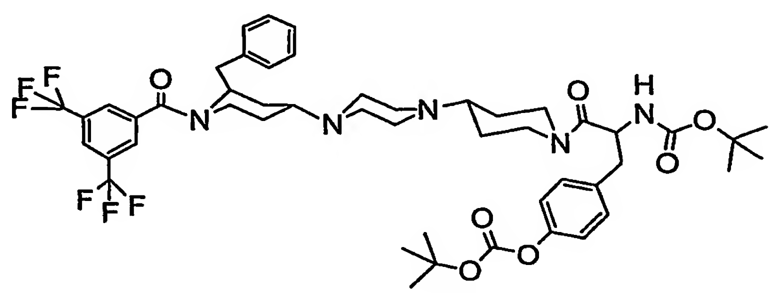
f. Preparation of intermediate compound 11



A mixture of intermediate compound 10 (0.0052 mol) in methanol (100ml) was hydrogenated at 50°C for one night with Pd/C, 10% (1g) as a catalyst. After uptake of H_2 (1eq), the catalyst was filtered off and the filtrate was evaporated. The residue was purified on a glass filter over silica gel (eluent : $CH_2Cl_2/(CH_3OH/NH_3)$ 99/1, 98/2, 97/3, 96/4 and 95/5). The pure fractions were collected and evaporated. Yielding : 1.7g on intermediate compound 11 (83%).

Example A4

Preparation of intermediate compound 12

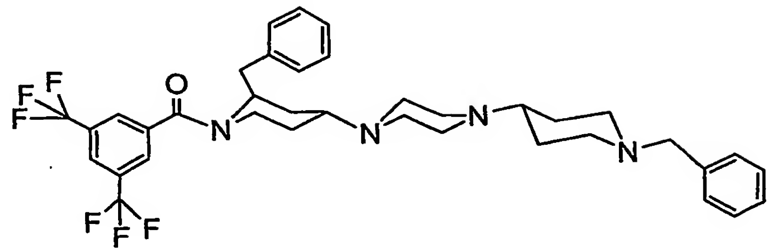


A mixture of *N*-[(1,1-dimethylethoxy)carbonyl]- L-Tyrosine 1,1-dimethylethyl carbonate ester (0.005 mol), *N,N*-dimethyl-4-pyridinamine (0.006 mol) and $(Et)_3N$ (10 ml) was stirred at room temperature. *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine monochloride (0.006 mol) was added portionwise and was stirred for 45 minutes at room temperature. Then final compound 2 (prepared according B1b) (0.005 mol) was added and the reaction mixture was stirred overnight at room temperature. The mixture was washed with H_2O and Na_2CO_3. The separated organic layer was dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: $CH_2Cl/MeOH$ 100/0; 98/2; 94/6). The purest fraction were collected and the solvent was evaporated. Yield: 1.4 g of intermediate compound 12 (30%).

Preparation of the final compounds

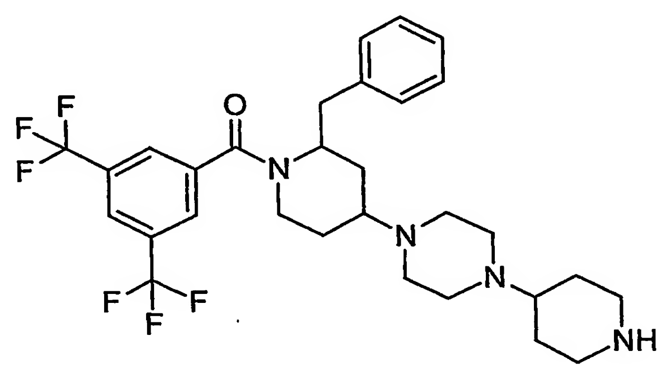
Example B1

a. Preparation of final compound 1



A mixture of intermediate compound 4 (0.12 mol) and 1-(phenylmethyl)-4-piperidinone (0.12 mol) in methanol (250ml) was hydrogenated (H163-066) at 50°C with Pd/C 10% (3g) as a catalyst in the presence of thiophene solution (2ml). After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was suspended in petroleum ether, filtered off and crystallized from DIPE. Yield : 46g (F1). The filtrate was evaporated. Yield : 37.7g (F2). F1 and F2 were combined and purified by column chromatography over silica gel (eluent : CH_2Cl_2/MeOH 91/9). The product fractions were collected and the solvent was evaporated. Yield : 46 g (F3). F3 was crystallized from DIPE. Yield : 0.65 g of final compound 1.

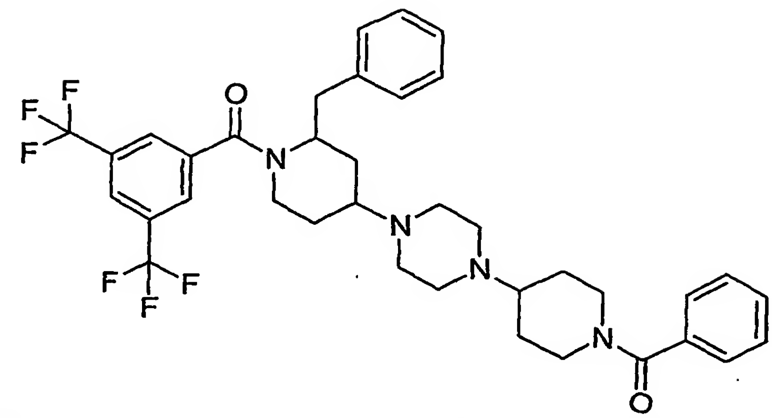
b. Preparation of final compound 2



A mixture of final compound 1 (0.0074 mol) in methanol (150ml) was hydrogenated (H163-077) with Pd/C 10% (1g) as a catalyst. After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was concentrated. Yield : 4.3g of final compound 2.

Example B2

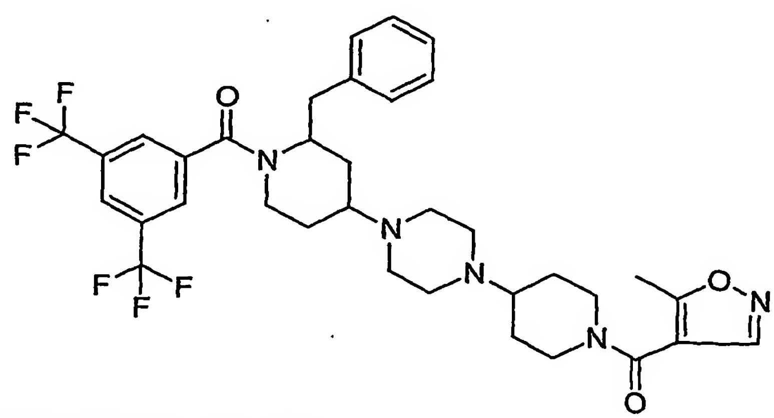
Preparation of final compound 3



A mixture of compound 2 (0.0015 mol) and Et_3N (0.1 mol) in CH_2Cl_2 (100ml) was stirred at room temperature. Benzoylchloride (0.0025 mol) was dissolved in CH_2Cl_2 and added dropwise to the reaction mixture. The mixture was stirred for 1 hour at room temperature. NaOH (1N;100ml) was added and the mixture was stirred for 30 minutes at room temperature. The separated aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/MeOH 100/0;90/10). The desired fractions were collected and the solvent was evaporated. Yield : 0.624g of final compound 3. (61%).

Example B3

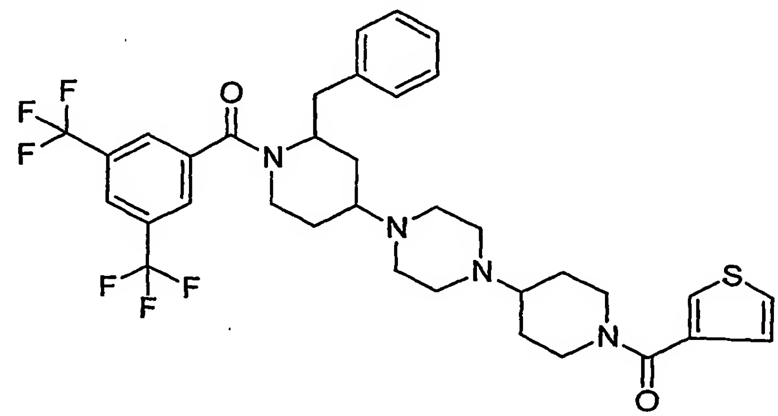
a. Preparation of final compound 4



A mixture of 5-methyl-4-isoxazolecarboxylic acid (0.0015 mol) in CH_2Cl_2 (20 ml) and 1,1'-carbonylbis-1*H*-imidazole (0.0015 mol) was stirred for 2 hours at room temperature. Compound 2 (prepared according to B1.b) (0.001 mol) was added. After stirring overnight, the reaction mixture was washed with diluted NaOH, washed with H_2O, dried, filtered and the solvent evaporated. The residue was purified by column

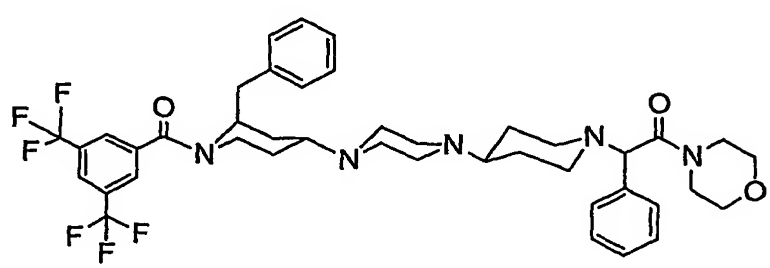
chromatography over silica gel (eluent: CH_2Cl_2 -gradient 0->10% MeOH).The product fractions were collected and the solvent evaporated. The residue was dried.
Yield : 0.204 g of final compound 4.

b. Preparation of final compound 5



A mixture of 3-thiophenecarboxylic acid (0.00188 mol), *N,N*-dimethyl-4-pyridinamine (0.00255 mol) and Et_3N (0.00255 mol) in CH_2Cl_2 (200 ml) was stirred at room temperature. *N,N*-dimethyl-*N'*-(methylcarbonimidoyl)-1,3-propanediamine (0.00255 mol) was added portionwise and the mixture was stirred for one hour at room temperature. A solution of compound 2 (prepared according to B1b) (0.00188 mol) in CH_2Cl_2 was added dropwise and the reaction mixture was stirred over the weekend at room temperature. The mixture was poured out into 1 g NaOH/water. The layers were separated. The water layer was extracted with CH_2Cl_2. The separated organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH from 100/0 to 90/10). The product fractions were collected and the solvent was evaporated. Yield: 0.749 g of compound 5 (58%).

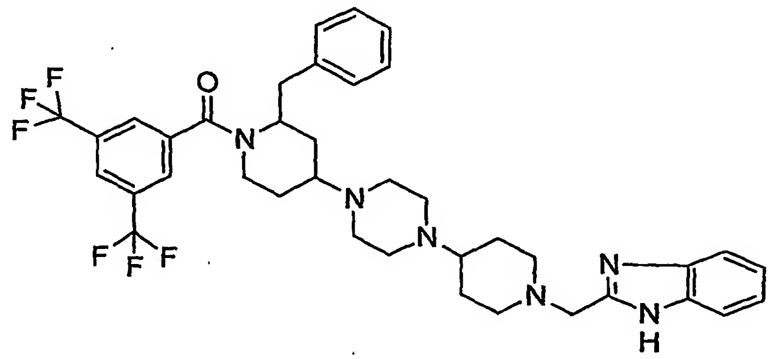
Example B4
a. Preparation of final compound 6



A mixture of compound 2 (prepared according to B1b) (0.005 mol), 4-(chlorophenylacetyl)-morpholine (0.005 mol) and Na_2CO_3 (0.01 mol) in MIK, p.a. (125 ml) was stirred and refluxed for 18 hours using a water separator. The reaction mixture was washed with water, dried, filtered and the solvent evaporated. The residue was

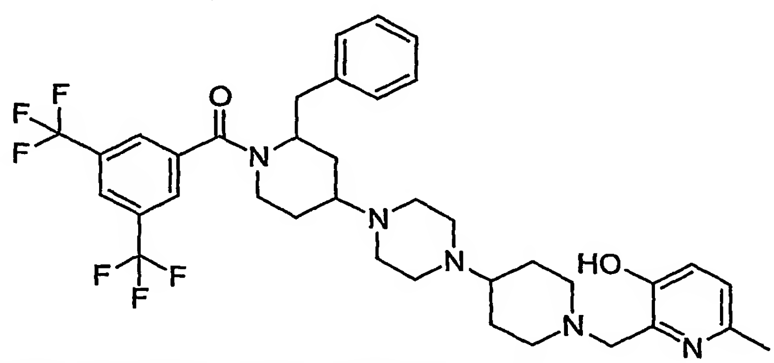
purified over silica gel on a glass filter (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 95/5). The product fractions were collected and the solvent was evaporated. The residue was suspended in DIPE, filtered off and dried. Yield: 1.702 g of compound 6.

b. Preparation of final compound 7



A mixture of compound 2 (prepared according to B1b) (0.0012 mol), 2-(chloromethyl)-1*H*-benzimidazole (0.0014 mol) and K_2CO_3 (0.0018 mol) in CH_3CN (5ml) was stirred and refluxed for 12 hours, then cooled to room temperature and the solvent was evaporated. The residue was taken up in CH_2Cl_2. The organic layer was washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (0.95g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 90/10/0.5; 15-40μm). The pure fractions were collected and the solvent was evaporated. The residue (0.14g) was crystallized from DIPE. The precipitate was filtered off and dried. Yielding: 0.087g of compound 7 (10%) (mp.135°C).

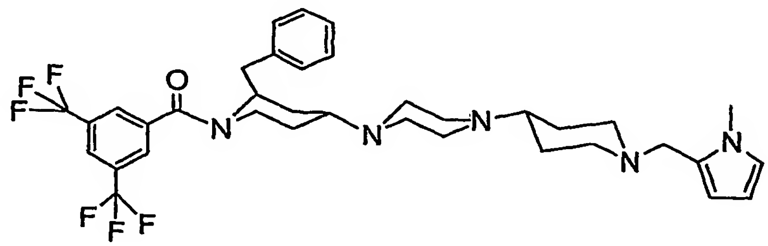
c. Preparation of final compound 8



A mixture of compound 2 (prepared according to B1b) (0.005 mol) and 2-(chloromethyl)-6-methyl-3-pyridinol (0.006 mol) was taken up in DMF (50ml). *N*-methyl-*N*-(1-methylethyl)-propanamine (0.02 mol) was added. The reaction mixture was stirred overnight at ±65°C. The solvent was evaporated. The residue was taken up in CH_2Cl_2 and washed with a diluted NH_3 solution. The separated organic layer was dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : $CH_2Cl_2/(MeOH/NH_3)$ 95/5). The desired

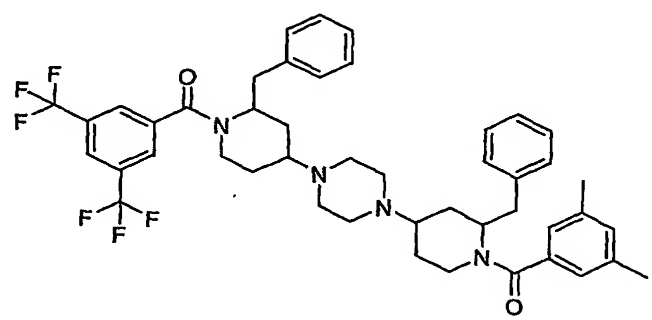
fractions were collected and the solvent was evaporated. The residue was suspended in DIPE. The precipitate was filtered off and dried. Yield : 1.423g of compound 8.

Example B5
Preparation of final compound 9



A mixture of compound 2 (prepared according to B1b) (0.003 mol) and 1-methyl-1*H*-pyrrole-2-carboxaldehyde (0.0046 mol) was hydrogenated at 50°C under H_2 with Pd/C 10% (1g) as a catalyst in the presence of thiophene solution (1ml). After uptake of H_2 (1 equiv.), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/($MeOH/NH_3$) 97/3;95/5). The product fractions were collected and the solvent was evaporated. The residue was suspended in petroleumether. Yield : 1.079g of compound 9.

Example B6
Preparation of final compound 10 and 11

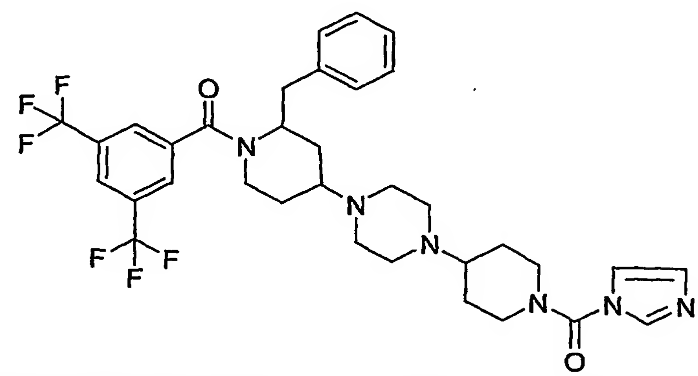


[2α,4α(2R*,4S*)]= compound 10
[2α,4β(2R*,4S*)]=compound 11

A mixture of intermediate compound 2 (prepared according to A1b) (0.005 mol), intermediate compound 11 (prepared according to A3f) (0.005 mol) and Ti(O*i*Pro)$_4$ (3g) in methanol (150ml) was hydrogenated at 50°C under N_2 flow with Pd/C 10% (1g) as a catalyst in the presence of thiophene solution (1ml). After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in H_2O and CH_2Cl_2. The mixture was stirred for 10 min and filtered over dicalite. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3)

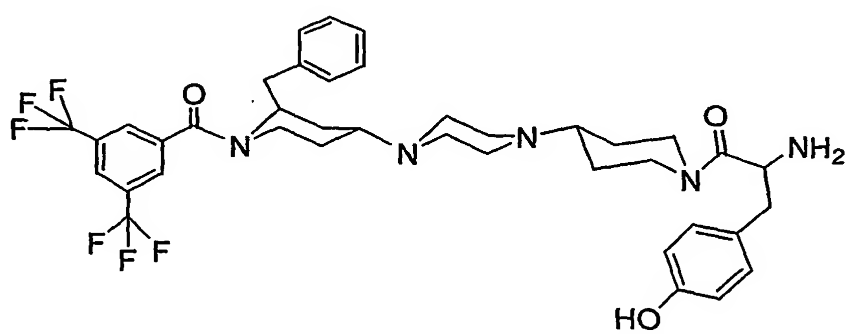
97/3). Two fractions were collected and their solvents were evaporated. Yielding: 0.53g compound 10 and 0.4g of compound 11.

Example B7
Preparation of final compound 12



A mixture of compound 2 (prepared according to B1b) (0.001 mol) in CH_2Cl_2 (50 ml) and C (0.0015 mol) was stirred overnight. The reaction mixture was washed with diluted NaOH, washed with H_2O, dried and the solvent was evaporated. The residue was purified by column chromatography over silica gel (Eluent: CH_2Cl_2/CH_3OH 100/0 and 90/10). The product fractions were collected and the solvent evaporated. Yield : 0.645 g of compound 12.

Example B8
Preparation of final compound 13

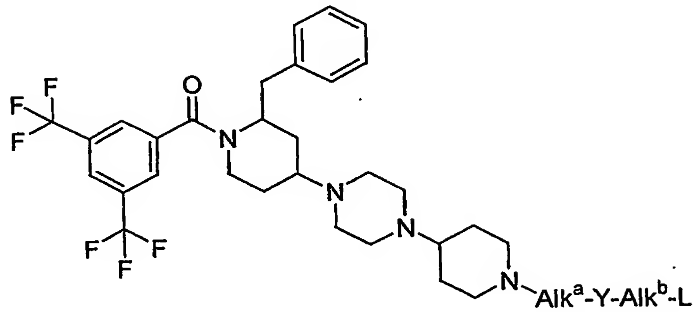


(2R-TRANS) Hydrochloride (1:3) Hydrate (1:1)

A mixture of intermediate compound 12 (prepared according to A4) (0.0015 mol) in HCl/2-propanol (5 ml) and methanol (20 ml) was stirred and refluxed for 1 hour. The reaction mixture was crystallized, filtered off and dried. Yield : 0.43 g of final compound 13 (38%)

The compounds exemplified in the following tables were prepared in a manner analogous to one of the foregoing examples B1 to B8.

Table 1



Comp No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Physical data
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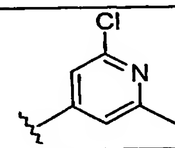
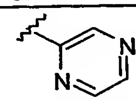
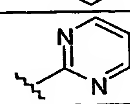
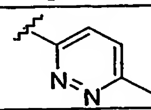
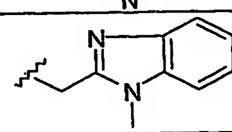
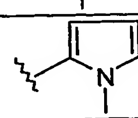
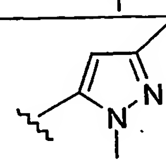
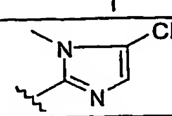
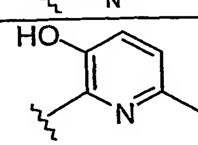
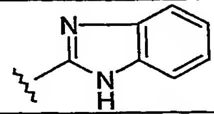
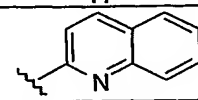
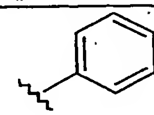
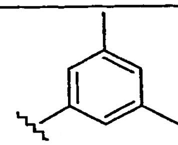
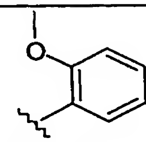
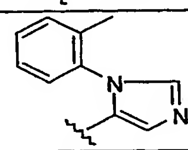
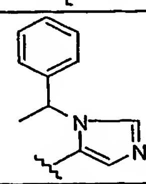
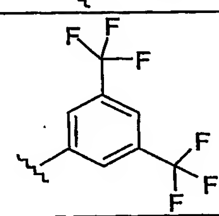
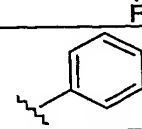
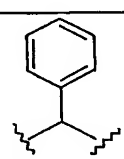
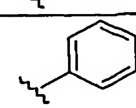
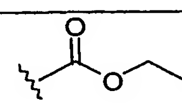
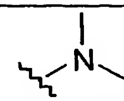
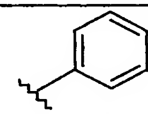
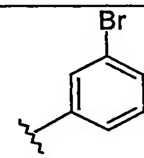
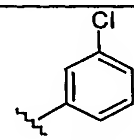
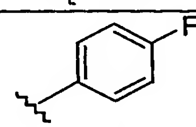
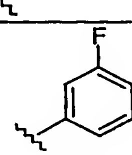
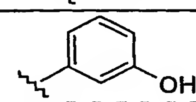
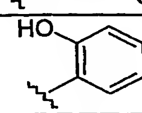
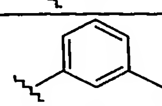
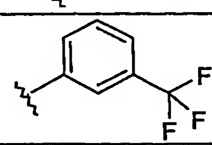
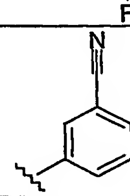
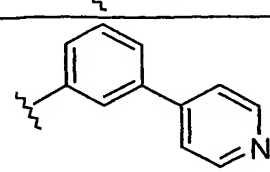
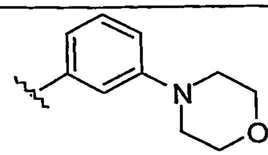
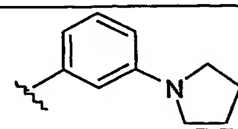
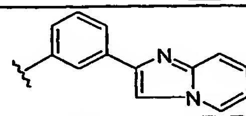
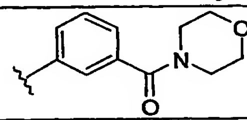
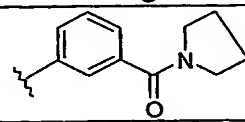
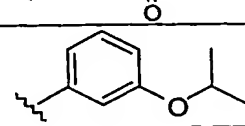
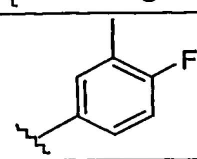
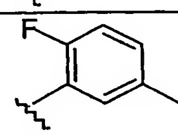
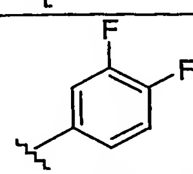
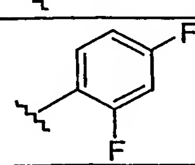
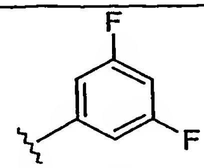
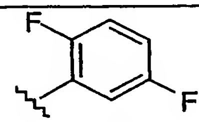
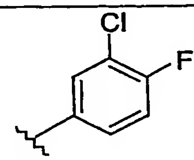
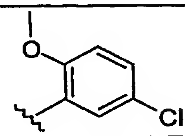
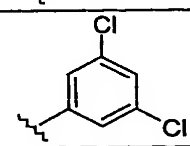
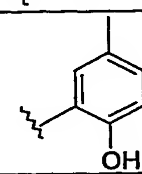
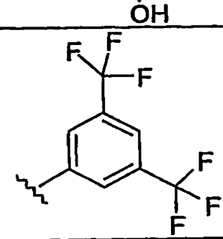
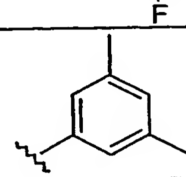
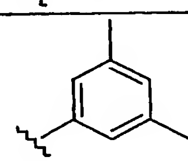
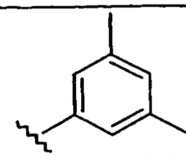
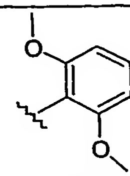
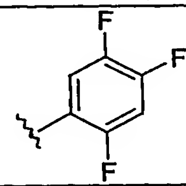
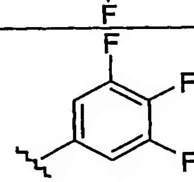
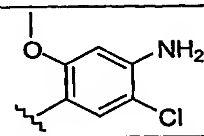
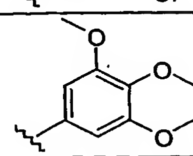
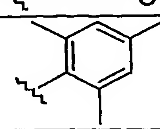
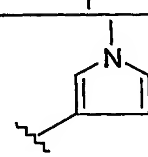
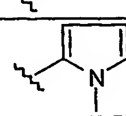
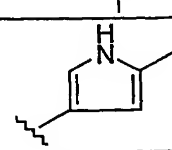
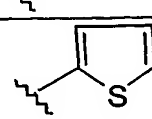
14		cb	cb	cb		2R-trans
15		cb	cb	cb		2R-trans
16		cb	cb	cb		2R-trans
17		cb	cb	cb		2R-trans
18		cb	cb	cb		2R-trans
9	B5	$-CH_2-$	cb	cb		2R-trans
19		$-CH_2-$	cb	cb		2R-trans
20		$-CH_2-$	cb	cb		2R-trans
8	B4c	$-CH_2-$	cb	cb		2R-trans

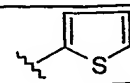
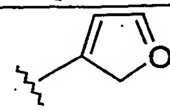
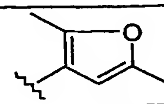
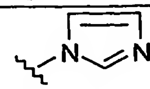
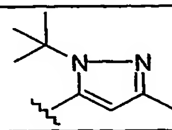
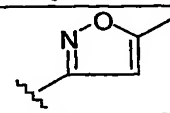
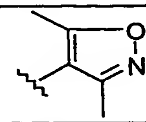
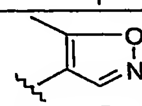
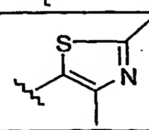
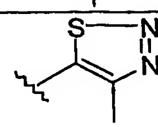
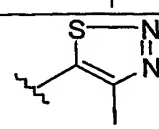
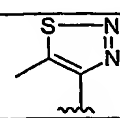
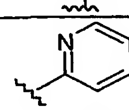
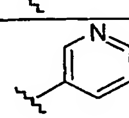
Comp No.	Exp. No.	Alk^a	Y	Alk^b	L	Physical data
7	B4b	-CH_2-	cb	cb		2R-trans
21		-CH_2-	cb	cb		2R-trans
1	B1a	-CH_2-	cb	cb		2R-trans
22		-CH_2-	cb	cb		2R-trans
23		-CH_2-	cb	cb		2R-trans
24		-CH_2-	cb	cb		2R-trans
25		-CH_2-	cb	cb		2R-trans
26		-CH_2-	cb	cb		2R-trans
27		-CH_2-CH=CH-	cb	cb		[2R-trans-[2α,4β(E)]]
28			cb	cb		2R-trans
29		cb	C=O	cb		2R-trans

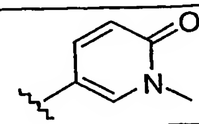
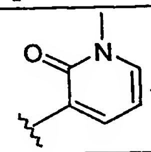
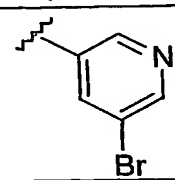
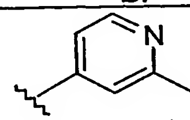
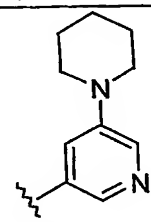
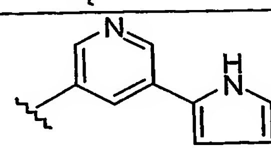
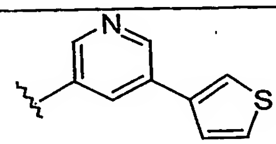
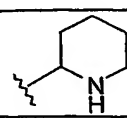
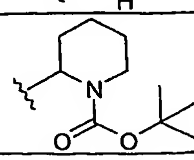
Comp. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Physical data
30		cb	C=O	cb		2R-trans
3	B2	cb	C=O	cb		2R-trans mp. 142.5°C
31		cb	C=O	cb		2R-trans
32		cb	C=O	cb		2R-trans
33		cb	C=O	cb		2R-trans
34		cb	C=O	cb		2R-trans
35		cb	C=O	cb		2R-trans
36		cb	C=O	cb		2R-trans
37		cb	C=O	cb		2R-trans
38		cb	C=O	cb		2R-trans
39		cb	C=O	cb		2R-trans
40		cb	C=O	cb		2R-trans

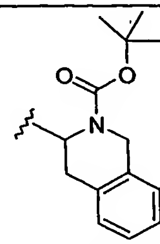
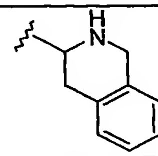
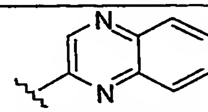
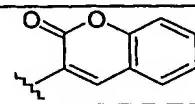
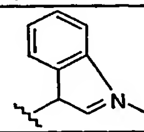
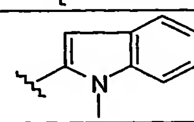
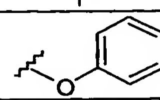
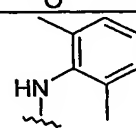
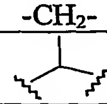
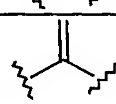
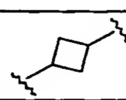
Comp. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Physical data
41		cb	C=O	cb		2R-trans
42		cb	C=O	cb		2R-trans
43		cb	C=O	cb		2R-trans
44		cb	C=O	cb		2R-trans
45		cb	C=O	cb		2R-trans
46		cb	C=O	cb		2R-trans
47		cb	C=O	cb		2R-trans
48		cb	C=O	cb		2R-trans
49		cb	C=O	cb		2R-trans
50		cb	C=O	cb		2R-trans

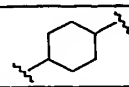
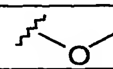
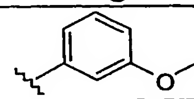
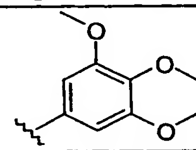
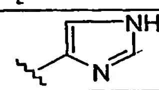
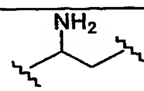
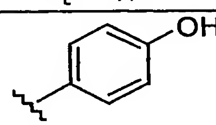
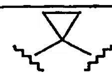
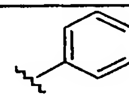
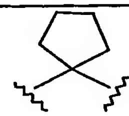
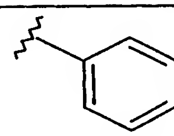
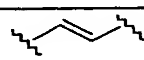
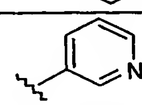
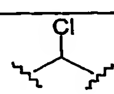
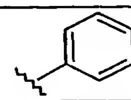
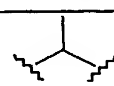
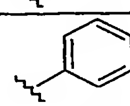
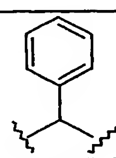
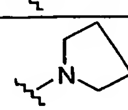
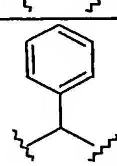
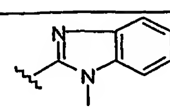
Comp. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Physical data
51		cb	C=O	cb		2R-trans
52		cb	C=O	cb		2R-trans
53		cb	C=O	cb		2R-trans
54		cb	C=O	cb		2R-trans
55		cb	C=O	cb		2R-trans
56		cb	C=O	cb		2R-trans
57		cb	C=O	cb		2R-trans
58		cb	C=O	cb		2R-trans
59		cb	C=O	cb		2R-trans

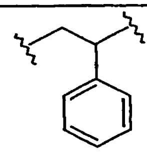
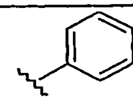
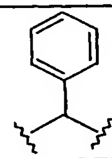
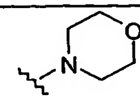
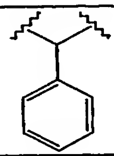
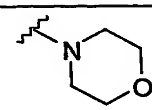
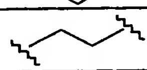
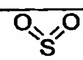
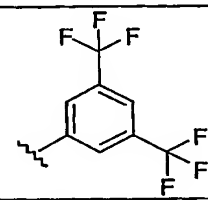
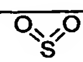
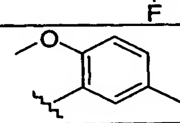
Comp. No.	Exp. No.	Alk^a	Y	Alk^b	L	Physical data
60		cb	C=O	cb		2R-trans
61		cb	C=O	cb		2R-trans
62		cb	C=O	cb		2R-trans
63		cb	C=O	cb		2R-trans
64		cb	C=O	cb		2R-trans
65		cb	C=O	cb		2R-trans
66		cb	C=O	cb		2R-trans
67		cb	C=O	cb		2R-trans
68		cb	C=O	cb		2R-trans
69		cb	C=O	cb		2R-trans
5	B3b	cb	C=O	cb		2R-trans

Comp. No.	Exp. No.	Alk^a	Y	Alk^b	L	Physical data
70		cb	C=O	cb		2R-trans
71		cb	C=O	cb		2R-trans
72		cb	C=O	cb		2R-trans
12	B7	cb	C=O	cb		2R-trans
73		cb	C=O	cb		2R-trans
74		cb	C=O	cb		2R-trans
75		cb	C=O	cb		2R-trans
4	B3a	cb	C=O	cb		2R-trans
76		cb	C=O	cb		2R-trans
77		cb	C=O	cb		2R-trans m.p. 119.6 °C
78		cb	C=O	cb		2R-trans; HCl(1:2); H_2O(1:1)
120		cb	C=O	cb		2R-trans
79		cb	C=O	cb		2R-trans
80		cb	C=O	cb		2R-trans

Comp No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Physical data
81		cb	C=O	cb		2R-trans
82		cb	C=O	cb		2R-trans
83		cb	C=O	cb		2R-trans
84		cb	C=O	cb		2R-trans
85		cb	C=O	cb		2R-trans
86		cb	C=O	cb		2R-trans
87		cb	C=O	cb		2R-trans
88		cb	C=O	cb		2R-trans
89		cb	C=O	cb		2R-trans

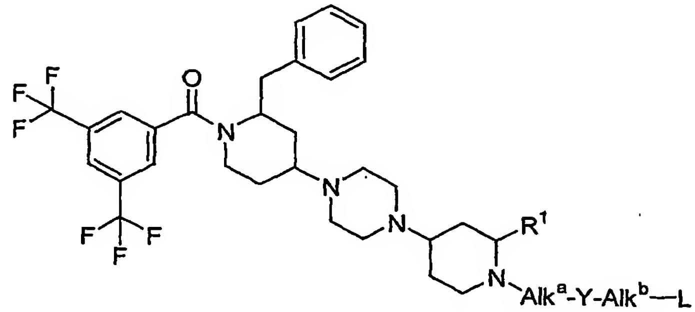
Comp No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Physical data
90		cb	C=O	cb		[2R-trans [2α,4β(S)]]
91		cb	C=O	cb		[2R-trans [2α,4β(S)]]
92		cb	C=O	cb		2R-trans
93		cb	C=O	cb		2R-trans
94		cb	C=O	cb		2R-trans
95		cb	C=O	cb		2R-trans
96		cb	C=O	cb		2R-trans
97		cb	C=O	cb		2R-trans
98		cb	C=O	$-CH_2-$	-H	2R-trans
99		cb	C=O		-H	2R-trans
100		cb	C=O		-H	2R-trans
101		cb	C=O		-H	2R-trans
102		cb	C=O		-H	2R-trans

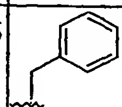
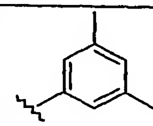
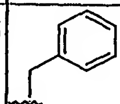
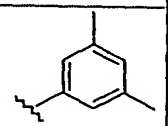
Comp. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Physical data
103		cb	C=O		-H	2R-trans
104		cb	C=O	$-CH_2-$		2R-trans
105		cb	C=O	$-CH_2-$		2R-trans
106		cb	C=O	$-CH_2-$		2R-trans
107		cb	C=O	$-CH_2-$		2R-trans
13	B8	cb	C=O			2R-trans, HCl(1:3); H_2O(1:1)
108		cb	C=O			2R-trans HCl(1:2) H_2O(1:1)
109		cb	C=O			2R-trans
110		cb	C=O			[2R-trans [2α,4β(E)]]
111		cb	C=O			2R-trans
112		cb	C=O			2R-trans
113		cb	C=O			2R-trans HCl(1:3) H_2O(1:3)
114		cb	C=O			2R-trans

Comp No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Physical data
115		cb	C=O			2R-trans
116		cb	C=O			2R-trans
6	B4a		C=O	cb		2R-trans
117			C=O	cb		2R-trans
118		cb		cb		2R-trans
119		cb		cb		2R-trans

cb = Covalent Bond

Table 2:



Co No.	Exp .No.	R^1	Alk^a	Y	Alk^b	L	Physical data
10	B6		cb	C=O	cb		[2α,4α(2R*,4S*)]
11	B6		cb	C=O	cb		[2α,4β(2R*,4S*)]

cb = Covalent Bond

C. Pharmacological example

Example C.1 : Binding experiment for h-NK_1, h-NK_2 and h-NK_3 receptors

The compounds according to the invention were investigated for interaction with various neurotransmitter receptors, ion channels and transporter binding sites using the radioligand binding technique. Membranes from tissue homogenates or from cells, expressing the receptor or transporter of interests, were incubated with a radioactively labelled substance ([^{3}H]- or [^{125}I] ligand) to label a particular receptor. Specific receptor binding of the radioligand was distinguished from the non-specific membrane labelling by selectively inhibiting the receptor labelling with an unlabelled drug (the blank), known to compete with the radioligand for binding to the receptor sites. Following incubation, labelled membranes were harvested and rinsed with excessive cold buffer to remove non-bound radioactivity by rapid filtration under suction. Membrane bound radioactivity was counted in a scintillation counter and results were expressed in counts per minute (cpm).

The compounds were dissolved in DMSO and tested at 10 concentrations ranging from 10^{-10} to 10^{-5} M.

The ability of the compounds according to the invention to displace [^{3}H]-Substance P from cloned human h-NK$_1$ receptors expressed in CHO cells, to displace [^{3}H]-SR-48968 from cloned human h-NK$_2$ receptors expressed in Sf9 cells, and to displace [^{3}H]-SR-142801 from cloned human h-NK$_3$ receptors expressed in CHO cells was evaluated.

The pIC$_{50}$ data for the h-NK$_1$, h-NK$_2$ and h-NK$_3$ receptor testing for a representative selection of compounds are presented in Table 3.

All selected compounds show (sub)nanomolar affinity for the h-NK$_1$ receptor most of them with more than 100-fold selectivity towards the h-NK$_2$ and h-NK$_3$ receptors.

Example C.2 : Signal transduction

This test evaluates in vitro functional NK$_1$ antagonistic activity. For the measurements of intracellular Ca^{++} concentrations the cells were grown on 96-well (black wall/transparent bottom) plates from Costar for 2 days until they reached confluence. The cells were loaded with 2 µM Fluo3 in DMEM containing 0.1% BSA and 2.5 mM probenecid for 1 h at 37°C. They were washed 3x with a Krebs buffer (140 mM NaCl, 1 mM $MgCl_2x6H_2O$, 5 mM KCl, 10 mM glucose, 5 mM HEPES; 1.25 mM $CaCl_2$; pH 7.4) containing 2.5 mM probenecid and 0.1 % BSA (Ca^{++}-buffer). The cells were preincubated with a concentration range of antagonists for 20 min at RT and Ca^{++}-signals after addition of the agonists were measured in a Fluorescence Image Plate Reader (FLIPR from Molecular Devices, Crawley, England). The peak of the Ca^{++}-transient was considered as the relevant signal and the mean values of corresponding wells were analysed as described below.

The sigmoidal dose response curves were analysed by computerised curve-fitting, using the GraphPad Program. The EC$_{50}$ -value of a compound is the effective dose showing 50 % of maximal effect. For mean curves the response to the agonist with the highest potency was normalised to 100 %. For antagonist responses the IC$_{50}$–value was calculated using non-linear regression.

Table 3

Co No.	h-NK$_1$ pIC$_{50}$	h-NK$_2$ pIC$_{50}$	h-NK$_3$ pIC$_{50}$
110	10.0	-	-
5	10.0	6.1	6.3
45	9.5	-	-

Co No.	h-NK1 pIC50	h-NK2 pIC50	h-NK3 pIC50
97	9.5	6.3	6.4
22	9.4	6.2	6.5
80	9.3	6.1	6.6
8	9.2	-	-
104	9.2	5.8	5.8
62	9.2	6.4	6.6
39	9.1	6.0	6.0
12	9.1	6.0	6.1
102	9.0	-	-
6	9.0	-	-
106	9.0	6.0	6.3
77	9.0	6.1	5.6
36	9.0	6.1	6.1
56	9.0	6.3	6.7
16	9.0	6.3	6.8
113	9.0	6.4	6.4
13	8.9	6.2	6.0
9	8.9	6.2	6.3
51	8.9	6.2	6.4
3	8.9	6.3	6.6
108	8.8	-	-
4	8.8	5.2	6.7
32	8.8	6.2	6.8
42	8.6	-	-
2	8.6	5.8	5.2
116	8.6	6.1	6.8
89	8.6	6.2	6.2
85	8.5	-	-
65	8.4	6.2	6.6
7	8.1	6.0	6.0
64	8.1	6.4	6.4
119	7.6	6.0	6.0
90	7.5	6.5	6.9
26	7.4	6.0	6.0

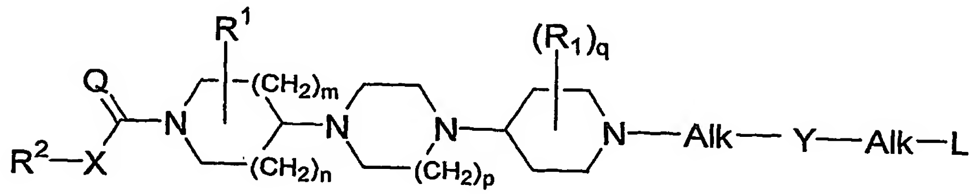
Co No.	h-NK_1 pIC_{50}	h-NK_2 pIC_{50}	h-NK_3 pIC_{50}
11	7.4	6.2	6.6
10	7.3	6.4	6.2

CLAIMS

1. The use of an NK_1-receptor antagonist for the manufacture of a medicament for the prevention and/or treatment of respiratory depression in opioid-based treatments of pain.

2. The use of an NK_1-receptor antagonist and an opioid analgesic for the manufacture of a medicament for the prevention and/or treatment of chronic neuropathic pain.

3. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredients, an opioid analgesic and a therapeutically effective amount of a compound according to Formula (I)



(I)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof, wherein :

n is an integer, equal to 0, 1 or 2 ;

m is an integer, equal to 1 or 2, provided that if m is 2, then n is 1 ;

p is an integer equal to 1 or 2 ;

Q is O or NR^3 ;

X is a covalent bond or a bivalent radical of formula -O-, -S- or $-NR^3-$;

each R^3 independently from each other, is hydrogen or alkyl ;

each R^1 independently from each other, is selected from the group of Ar^1, Ar^1-alkyl and di(Ar^1)-alkyl ;

q is an integer equal to 0 or 1 ;

R^2 is alkyl, Ar^2, Ar^2-alkyl, Het^1 or Het^1-alkyl ;

Y is a covalent bond or a bivalent radical of formula -C(=O)- or $-SO_2-$;

each Alk represents, independently from each other, a covalent bond; a bivalent straight or branched, saturated or unsaturated hydrocarbon radical having from 1 to 6 carbon atoms ; or a cyclic saturated or unsaturated hydrocarbon radical having from 3 to 6 carbon atoms ; each radical

optionally substituted on one or more carbon atoms with one or more alkyl, phenyl, halo, cyano, hydroxy, formyl and amino radicals ;

L is selected from the group of hydrogen, alkyloxy, Ar^3-oxy, alkyloxycarbonyl, mono- and di(alkyl)amino, mono-and di(Ar^3)amino, Ar^3, Ar^3-carbonyl, Het^2 and Het^2-carbonyl;

Ar^1 is phenyl, optionally substituted with 1, 2 or 3 substituents each independently from each other selected from the group of halo, alkyl, cyano, aminocarbonyl and alkyloxy ;

Ar^2 is naphthalenyl or phenyl, each optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, nitro, amino, mono- and di(alkyl)amino, cyano, alkyl, hydroxy, alkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl and mono- and di(alkyl)aminocarbonyl ;

Ar^3 is naphthalenyl or phenyl, optionally substituted with 1, 2 or 3 substituents each independently from each other selected from the group of alkyloxy, alkyl, halo, hydroxy, pyridinyl, morpholinyl, pyrrolidinyl, imidazo[1,2-*a*]pyridinyl, morpholinylcarbonyl, pyrrolidinylcarbonyl, amino and cyano;

Het^1 is a monocyclic heterocyclic radical selected from the the group of pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl ; or a bicyclic heterocyclic radical selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl ; each heterocyclic radical may optionally be substituted on any atom by a radical selected from the group of halo and alkyl ;

Het^2 is a monocyclic heterocyclic radical selected from the group of pyrrolidinyl, dioxolyl, imidazolidinyl, pyrrazolidinyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, imidazolidinyl, tetrahydrofuranyl, 2H-pyrrolyl, pyrrolinyl, imidazolinyl, pyrrazolinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl ; or a bicyclic heterocyclic radical selected from the group of benzopiperidinyl, quinolinyl, quinoxalinyl, indolyl, isoindolyl, chromenyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl ; each radical

optionally substituted with one or more radicals selected from the group of Ar^1, Ar^1alkyl, halo, hydroxy, alkyl, piperidinyl, pyrrolyl, thienyl, oxo, alkyloxy, alkyloxyalkyl and alkyloxycarbonyl ; and

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radicals having from 3 to 6 carbon atoms ; optionally substituted on one or more carbon atoms with one or more radicals selected from the group of phenyl, halo, cyano, oxo, hydroxy, formyl and amino radicals.

4. A pharmaceutical composition according to claim 3, characterized in that

n is 1 ;

m is 1 ;

p is 1 ;

Q is O ;

X is a covalent bond ;

each R^1 is Ar^1 or Ar^1-alkyl ;

q is 0 or 1 ;

R^2 is Ar^2 ;

Y is a covalent bond or a bivalent radical of formula -C(=O)- or $-SO_2-$;

each Alk represents, independently from each other, a covalent bond; a bivalent straight or branched, saturated or unsaturated hydrocarbon radical having from 1 to 6 carbon atoms ; or a cyclic saturated or unsaturated hydrocarbon radical having from 3 to 6 carbon atoms ; each radical optionally substituted on one or more carbon atoms with one or more phenyl, halo, cyano, hydroxy, formyl and amino radicals ;

L is selected from the group of hydrogen, alkyloxy, Ar^3-oxy, alkyloxycarbonyl, mono- and di(alkyl)amino, mono-and di(Ar^3)amino, Ar^3 and Het^2;

Ar^1 is phenyl, optionally substituted with 1, 2 or 3 alkyl radicals ;

Ar^2 is phenyl, optionally substituted with 1, 2 or 3 alkyl radicals ;

Ar^3 is phenyl, optionally substituted with 1, 2 or 3 substituents each independently from each other selected from the group of alkyloxy, alkyl, halo, hydroxy, pyridinyl, morpholinyl, pyrrolidinyl, imidazo[1,2-*a*]pyridinyl, morpholinylcarbonyl, pyrrolidinylcarbonyl, amino and cyano ;

Het^2 is a monocyclic heterocyclic radical selected from the group of pyrrolidinyl, piperidinyl, morpholinyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, isoxazolyl, thiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl ; or a bicyclic heterocyclic radical selected from the group of

benzopiperidinyl, quinolinyl, quinoxalinyl, indolyl, chromenyl and benzimidazolyl ; each radical optionally substituted with one or more radicals selected from the group of Ar^1, Ar^1alkyl, halo, hydroxy, alkyl, piperidinyl, pyrrolyl, thienyl, oxo and alkyloxycarbonyl ; and

alkyl is a straight hydrocarbon radical having 1 to 6 carbon atoms, optionally substituted with one or more halo radicals .

5. A pharmaceutical composition according to any of claims 3 to 4, characterized in that R^1 is Ar^1methyl and attached to the 2-position or R^1 is Ar^1 and attached to the 3-position.

6. A pharmaceutical composition according to any of claims 3 to 5, characterized in that the R^2-X-C(=Q)- moiety is 3,5-di-(trifluoromethyl) phenylcarbonyl.

7. A pharmaceutical composition according to any of claims 3 to 6, characterized in that the compound according to Formula (I) is a compound with compound number 110, 5, 45, 97, 22, 80, 8, 104, 62, 39, 12, 102, 6, 106, 77, 36, 56, 16, 113, 13, 9, 51, 3, 108, 4, 32, 42, 2, 116, 89, 85, 65, 7, 64, 119, 90, 26, 11 and 10 as cited in Table 3.

8. A pharmaceutical product comprising a compound according to Formula (I) and an opioid as a combined preparation for simultaneous, separate or sequential use.

9. A pharmaceutical composition or product according to any of claims 3 to 8, characterized in that the opioid analgesic is selected from the group of alfentanil, buprenorphine, butorphanol, codeine, diacetylmorphine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propoxyphene and sufentanyl; or a pharmaceutical acceptable salt thereof.

10. A pharmaceutical composition or product according to claim 9, characterized in that the opioid analgesic is selected from the group of fentanyl and morphine.

11. A pharmaceutical composition or product according to any of claims 3 to 10, characterized in that it is in a form suitable to be orally administered.

12. The use of a pharmaceutical composition or product according to any one of

claims 3-11 for the manufacture of a medicament for the prevention and/or treatment of pain and/or nociception.

13. The use of a pharmaceutical composition or product according to any one of claims 3-11 for the manufacture of a medicament for the prevention and/or treatment of chronic neuropathic pain.

14. The use of a pharmaceutical composition or product according to any one of claims 3-11 for the manufacture of a medicament for the prevention and/or treatment of emesis in opioid-based treatments of pain.

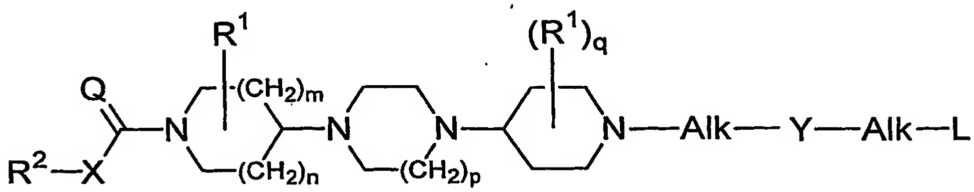
15. The use of an NK_1-receptor antagonist according to Formula (I) for the manufacture of a medicament for the prevention and/or treatment of respiratory depression in opioid-based treatments of pain.

ABSTRACT

NOVEL FORMULATIONS FOR OPIOID-BASED TREATMENTS OF PAIN COMPRISING SUBSTITUTED 1,4-DI-PIPERIDIN-4-YL-PIPERAZINE DERIVATIVES.

The invention concerns novel formulations for opioid-based treatments of pain and/or nociception comprising opioid analgesics and 1,4-di-piperidin-4-yl-piperazine derivatives having tachykinin antagonistic activity, in particular NK_1 antagonistic activity and their use for the manufacture of a medicament for the prevention and/or treatment of pain and.or nociception, in particular chronic neuropathic pain and the treatment of respiratory depression and/or emesis.

The pharmaceutical formulations according to the invention comprise NK_1-antagonists according to the general Formula (I)



(I)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof, wherein all substituents are defined as in Claim 1.

The pharmaceutical composition according to the invention reduces to a large extent a number of unwanted side-effects associated with opioid analgesics, thereby increasing the total tolerability of said opioids in pain treatment.

The invention is further concerned with the use of an NK_1-receptor antagonist for the manufacture of a medicament for the prevention and/or treatment of respiratory depression in opioid-based treatments of pain as well as with the use of an NK_1-receptor antagonist and an opioid analgesic for the manufacture of a medicament for the prevention and/or treatment of chronic neuropathic pain.